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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/091,591	03/07/2002	Raymond J. Bergeron	T2315-907789	9684

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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
02/27/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/091,591	BERGERON, RAYMOND J.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-6 are presented for examination

Applicant's amendment filed 11/26/2007 has been received and entered into the application. Accordingly, claim 1 has been amended.

Applicant's arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Response to Arguments

Applicant's arguments filed 11/26/2007 have been fully considered but they are not persuasive. Applicant presents the following arguments with respect to the rejections set forth in the Non-Final Office Action mailed 8/28/2007.

Firstly, with respect to the 35 U.S.C. § 112, 1st Paragraph rejection of claims 1-6 as lacking written basis for the *proviso* excluding the *trans* isomer of CHX(4,4,4-*trans*) (*i.e.*, the second compound recited in claim 1), Applicant argues, citing *Ex parte Parks* and *Ex parte Grasselli*, that a lack of literal basis in the specification for a negative limitation is not sufficient to establish a *prima facie* case for lack of descriptive support. However, while it is true that Applicant is not required to literally disclose in the specification that the *trans* isomers of the claimed compounds are excluded, in the instant case there is no positive recitation of the compound CHX(4,4,4-trans) in the originally filed disclosure. As such, because this compound is neither positively nor negatively recited in the originally filed disclosure, there is no written

basis for excluding it from the claims. The rejection is maintained for the reasons of record and reiterated below.

Secondly, with respect to the 35 U.S.C. § 102(b) rejection of claims 1-2 and 4-5 as being anticipated by Frydman *et al.*, Applicant argues that the claims have been amended to exclude compounds of Formula (I) and (II) wherein Q is either a 3 or 4 membered cycloalkyl ring. This argument is persuasive because the Frydman *et al.* only exemplify compound species having a 3 or 4 membered cycloalkyl ring, which are no longer encompassed by the instant claims. However, Applicant's amendment to claim 1 has necessitated new grounds of rejection under both 35 U.S.C. § 112, 1st Paragraph (New Matter) and 35 U.S.C. § 103 (see below).

Thirdly, with respect to the 35 U.S.C. § 103 rejection of claims 3 and 6 (now claims 1-6) as being unpatentable over Frydman *et al.*, Applicant asserts that the Examiner has overlooked the fact that the present claims are directed to "anti-diarrheal or gastrointestinal anti-spasmodic pharmaceutical composition" comprising an "effective amount" of the requisite compound (emphasis in original). However, the intended use of a pharmaceutical composition is not given patentable weight if the prior art teaches or suggests a pharmaceutical composition comprising the same compound(s), but for a different purpose. In this case, Frydman *et al.* teach pharmaceutical compositions comprising compounds encompassed by the instantly claimed genus and teaches that such compositions are useful for treating cancer (see Table 1 and Table 2). As such, it would have been *prima facie* obvious to formulate a pharmaceutical composition comprising a compound of Formula (I) as recited in the instant claims. Whether such a composition is used to treat cancer (as taught in Frydman *et al.*) or is used as an anti-diarreal or gastrointestinal anti-sposmodic (as instantly claimed) is not pertinent to the present rejection.

MAINTAINED REJECTION

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are again rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

No support is seen in the specification for the *proviso*, "excluding the *trans* isomers of the compounds having the structures...." as recited in claim 1. The first excluded compound is CHX(3,4,3-*trans*), which is positively recited at pages 8 and 14 of the specification. This is the **only** specific compound identified in the specification. The second excluded compound is CHX(4,4,4-*trans*), which is neither positively nor negatively recited in the specification. Accordingly, Applicant has no written basis for the specific exclusion of CHX(4,4,4-*trans*) from the claims.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

> pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

In the amendment to the claims filed 11/26/2007, claim 1 was amended to recite the limitation wherein "Q is a cycloalkyl group having from 5 to 10 carbon atoms". Previously presented claim 1 had the limitation wherein Q is a cycloalkyl group having from 3 to 10 carbon atoms. No support is found in the originally filed disclosure for cycloalkyl groups having from 5 to 10 carbon atoms as recited in the instant claims. The only specific compound disclosed contains a cyclohexyl group (*i.e.*, 6 carbon atoms). There are no compounds recited in the original disclosure that would provide support for the limitation of Q being a cycloalkyl group having from 5 to 10 carbon atoms.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **Frydman *et al.*** (U.S. Patent No. 5,889,061; Issued Mar. 30, 1999).

The instant claims recite pharmaceutical compositions comprising an effective amount of a compound having the formula:

(I)

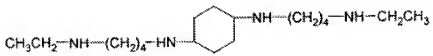
wherein: R_1, R_2, R_3 and R_4 are the same or different and are H, alkyl, cycloalkyl or aralkyl having from 1 to 12 carbon atoms, or a heterocyclic group having from 3 to 10 atoms wherein the hetero atom is said N^1 or N^2;

Q is a cycloalkyl group having from 3 to 10 carbon atoms;

x is an integer from 3 to 6, inclusive;

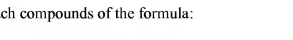
excluding the *trans* isomers of the compounds having the structures:

and



and a pharmaceutically acceptable carrier. Instant claim 3 recites the limitation wherein Q is cyclohexyl in the compounds of Formula I. Claim 6 recites the limitation wherein Q is cyclohexyl; x and y are 3; R_1 and R_3 are both H, and R_2 and R_4 are both ethyl. Other dependent claims recite limitations wherein: Q is connected either *cis* or *trans* as the (1,2), (1,3), (1,4), (1,5) or (1,6) isomer (claim 2); x is 3 and y is 3 (claim 4); and x is 3, y is 3, R_1 and R_3 are both H and R_2 and R_4 are both ethyl (claim 5).

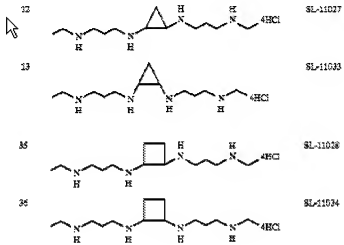
Frydman *et al.* teach compounds of the formula:



E-NH-D-NH-B-A-B-NH-D-NH-E (I)

wherein A is C_3–C_7 alkene, C_3–C_7 cycloalkyl, cycloalkenyl, or cycloaryl; B is independently a single bond, C_1–C_7 alkyl alkenyl; D is independently C_1–C_6 alkyl or alkenyl, or C_3–C_6 cycloalkyl, cycloalkenyl, or cycloaryl; and E is independently H, C_1–C_3 alkyl or alkenyl; and

and pharmaceutically acceptable salts thereof (Abstract; col. 2, lines 1-11). Exemplified compounds of the invention are taught in Table 1.



Instant claim 2 recites the limitation wherein Q is connected either *cis* or *trans* as the (1,2) isomer. The above compounds are connected *cis* (SL-11033 and SL-11034) and *trans* (SL-11027 and SL-11028) as the (1,2) isomer, thus teaching the limitations of claim 2.

Pharmaceutical compositions comprising the compounds of the invention in a pharmaceutically acceptable carrier and in an effective amount are taught at column 21, line 3 to column 22, line 9. For example, Frydman *et al.* teach formulating the compounds of the invention in pharmaceutically acceptable carriers (col. 21, lines 35-44 and lines 52-55).

It is well established that intended use does not impart patentability in a composition claim. See *In re Zierden*, 411 F.2d 1325, 1329, 162 USPQ 102, 104 (CCPA 1969):

> A mere statement of a new use for an otherwise old or obvious composition cannot render a claim to the composition patentable. As we said in *In re Lemin*, 51 CCPA 942,326 F.2d 437,140 USPQ 273,276 (1964),
>
> > Appellants are clearly correct in demanding that the subject matter as a whole must be considered under 35 U.S.C. 103. But in applying the statutory test, the differences over the prior art must be more substantial than a statement of the intended use of an old composition. ... It seems to us that the composition ... would be exactly the same whether the user were told to cure pneumonia in animals with it ... or to promote plant growth with it (as here). The directions on the label will not change the composition....

See also, *In re Spada*, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990) ("[t]the discovery of a new property or use of a previously known composition, even when that property and use are unobvious from the prior art, cannot impart patentability to claims to the known composition"). Accordingly, the claims simply require a composition comprising a compound of formula I and a pharmaceutically acceptable carrier. As such, the compositions of Frydman *et al*. render *prima facie* obvious the instantly claimed compositions.

Frydman *et al*. differ from the instant claims in that they do not explicitly exemplify compounds wherein the C_3-C_6 cycloalkyl is cyclohexyl. Exemplified compounds of the invention are drawn to cyclopropyl and cyclobutyl moieties (Table 1). However, Frydman *et al*. teach that "A" (Q in the instant claims) can be C_2-C_6 alkene, C_3-C_6 cycloalkyl, cycloalkenyl, or cycloaryl (Abstract). Thus, with respect to cycloalkyl groups, there are only four possible substitutions: cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. The inventors made and exemplified cyclopropyl and cyclobutyl substituted compounds (Table 1) having identical substituents as those recited in instant claim 6 (*i.e*., x and y are 3; R_1 and R_3 are both H, and R_2 and R_4 are both ethyl).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Scope and Content of the Prior Art:

In the instant case, Frydman *et al.* teach a genus of compounds having a limited number of alternate substitutions. With respect to the instantly claimed sub genus of compounds having a cyclohexyl group, Frydman *et al.* teach that the compounds of the invention can be substituted with a C_3-C_6 cyclohexyl (four possible substitutions). The compounds of Frydman *et al.* are taught to be useful in the treatment of cancer. In this regard, compounds having a cyclopropyl (C_3) and cyclobutyl (C_4) substitution were exemplified and tested for anticancer activity (Table 1 and Table 2). The number of species encompassed by the genus taught in Frydman *et al.* is relatively small. For example, there are only twelve possible substitutions for A, eight for B, eighteen for D, and thirteen for E. The majority of these substitutions are structurally related and represent homologous series (*e.g.*, C_2-C_6 alkene, C_3-C_6 cycloalkyl, C_1-C_6 alkyl, etc.).

Differences Between Prior Art and Claims:

The closest disclosed prior art species to the sub genus instantly claimed are the compounds designated SL-11027, SL-11033, SL-11028, and SL-11034 in Frydman *et al.* (Table

1). These species differ from the instantly claimed genus **only** in the number of carbons present in the cycloalkyl substitution (*i.e.*, C_3 and C_4 versus C_6); all other substituents are identical.

Level of Ordinary Skill in the Art:

A person having ordinary skill in the art at the time of the present invention would generally be a medical chemist well practiced in the art of structure-activity relationships as they pertain to chemical modifications and biological activity.

Objective Evidence and Motivation:

In light of the above findings relating to the three *Graham* factors, the skilled artisan would have been motivated to make the claimed sub genus of compounds and to formulate them in a pharmaceutical composition. See, *e.g.*, *Deuel*, 51 F.3d at 1557, 34 USPQ2d at 1214 ("[A] *prima facie* case of unpatentability requires that the teachings of the prior art suggest *the claimed compounds* to a person of ordinary skill in the art." (emphasis in original)); *In re Lalu*, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984) ("The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound."). Considering the size of the prior art genus, especially with respect to the limited number of cycloalkyl groups contemplated by Frydman *et al.*, one skilled in the art could readily envisage each member of the sub genus of compounds containing C_3-C_6 cycloalkyl groups. *In re Petering*, 301 F.2d 676, 681, 133 USPQ 275, 280 (CCPA 1962). Frydman *et al.* also expressly suggest and motivate the selection of a cyclohexyl substitution. For example, cyclopropyl and cyclobutyl groups introduce constraints into otherwise flexible spermine

molecules (col. 4, lines 53-67) and a "cyclohexyl moiety" can be introduced *in a similar manner* to the cyclopropyl and cyclobutyl constraints (col. 5, lines 6-7). The skilled artisan would recognize that the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl series of homologs could be used to evaluate conformational constraints in spermine analogs (*i.e.*, cyclopropyl provides the most constraint whereas cyclohexyl provides the least constraint). As such, making cyclopentyl and cyclohexyl substituted spermine analogs having the same substituents as the explicitly disclosed cyclopropyl and cyclobutyl analogs would be the next logical step.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art to also make the cyclopentyl- and cyclohexyl-substituted compounds and to formulate them into pharmaceutical compositions. This is especially true given the limited number of cycloalkyl substituents contemplated in Frydman *et al.* (*i.e.*, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl). Two of these four cycloalkyls were exemplified in the reference. Accordingly, the skilled artisan would have been highly motivated to choose the instantly claimed cyclohexyl substitution, based on the reasonable expectation that structurally similar species usually have the same properties. See, *e.g.*, *Dillon*, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also *Deuel*, 51 F.3d at 1558, 34 USPQ2d at 1214 ("Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties.").

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614